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A role of gamma-amino butyric acid (GABA) and glutamate in control of puberty in female rhesus monkeys: effect of an antisense oligodeoxynucleotide for GAD67 messenger ribonucleic acid and MK801 on luteinizing hormone-releasing hormone release.

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Previously we have shown that gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter restricting the pubertal increase in LHRH release in juvenile monkeys, and that interfering with GABA synthesis with an antisense oligodeoxynucleotide (AS) for glutamic acid decarboxylase (GAD67) mRNA results in an increase in LHRH release in prepubertal monkeys. GAD67 is a catalytic enzyme that synthesizes GABA from glutamate. To further clarify the role of GABA in puberty, we examined whether the inhibition of LHRH release by GABA continues after the onset of puberty and whether input from glutamatergic neurons plays any role in the onset of puberty when GABA inhibition declines, using a push-pull perfusion method. In Study I, the effects of the AS GAD67 mRNA on LHRH release in pubertal monkeys (34.3 +/- 1.5 months of age, n = 8) were examined, and the results were compared with those in prepubertal monkeys (18.5 +/- 0.4 months, n = 12). Direct infusion of AS GAD67 (1 microM) into the stalk-median eminence (S-ME) for 5 h stimulated LHRH release in both prepubertal and pubertal monkeys. However, the increase in LHRH release in pubertal monkeys was significantly ($P < 0.01$) smaller than that in prepubertal monkeys. Infusion of a scrambled oligo as a control was without effect in either group. In Study II, to examine the possibility that an increase in glutamate tone after the reduction of an inhibitory GABA tone contributes to the AS GAD67-induced LHRH increase, the effects of the NMDA receptor blocker MK801 (5 microM) on LHRH release were tested in monkeys treated with AS GAD67. MK801 infusion into the S-ME during the treatment of AS GAD67 (1 microM) suppressed the AS GAD67-induced LHRH release in both age groups. MK801 alone did not cause any significant effect in either group. The data are interpreted to mean that GABA continues to suppress LHRH release after the onset of puberty, although the degree of suppression is weakened considerably after the onset of puberty, and that the increased LHRH release after AS GAD67 treatment may be partly due to an increase in glutamate tone mediated by NMDA receptors, as well as due to the decrease in GABA release following the decrease in GAD synthesis. Taken together, the present results suggest that GAD may play an important role in the onset and progress of puberty in nonhuman primates.

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Growth factor deprivation therapy of hormone insensitive prostate and breast cancers utilizing antisense oligonucleotides.

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Antisense oligonucleotides (oligos) are artificial sequences of nucleotide bases which may be synthesized complementary to known regions within specific mRNAs. When these constructed oligos interact with protein encoding mRNA they may regulate expression of various growth factors and/or their receptors. Oligos directed against transforming growth factor-alpha (TGF-alpha) and its binding site, the epidermal growth factor receptor (EGFR), were employed: A) in vitro to affect the growth of hormone insensitive human derived PC-3 prostate cancer cells as well as the human derived UACC-893 breast cancer cell line; and B) in vivo to treat tumors established by these cell lines in athymic nude mice. The in vitro results for each oligo, and their combination, produced significant inhibition of both prostate and breast cell lines. In addition, the combination of oligos most efficiently diminished the immunohistochemical expression of both TGF-alpha and EGFR in PC-3 cells. Direct in vivo inoculation of oligos into established PC-3 or UACC-893 tumors in nude mice produced hemorrhagic necrosis within 2-3 days. Such therapy could represent a new tier of therapy for recurrent, hormone insensitive, tumors based upon the concept of growth factor deprivation.

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